PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 237/32, A61K 31/495 | A1

(11) International Publication Number: WO 99/31071

(43) International Publication Date: 24 June 1999 (24.06.99)

(21) International Application Number: PCT/EP98/08015

(22) International Filing Date: 9 December 1998 (09.12.98)

(30) Priority Data:
97122038.9 15 December 1997 (15.12.97) EP

(71) Applicant *(for all designated States except US)*: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk–Gulden–Strasse 2, D–78467 Konstanz (DE).

(72) Inventors *(for all designated States except CA US)*: HATZELMANN, Armin; Alter Wall 3, D–78467 Konstanz (DE). BOSS, Hildegard; Flurweg 3a, D–78464 Konstanz (DE). HÄFNER, Dietrich; Beethovenstrasse 5, D–78464 Konstanz (DE). BEUME, Rolf; Bohlstrasse 13, D–78465 Konstanz (DE). KLEY, Hans–Peter; Im Weinberg 3b, D–78476 Allensbach (DE). VAN DER MEY, Margaretha; Hoefblad 59, NL–2231 WP Rijnsburg (NL). VAN DER LAAN, Ivonne, Johanna; Nieuwstraat 44, NL–2266 AE Leidschendam (NL). TIMMERMAN, Hendrik; De Savornin Lohmanplantsoen 3, NL–2253 VM Voorschoten (NL).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: STERK, Geert, Jan [NL/NL]; Stadhouderslaan 38, NL–3583 JJ Utrecht (NL).

(74) Common Representative: BYK GULDEN; Lomberg Chemische Fabrik GmbH, Byk–Gulden–Strasse 2, D–78467 Konstanz (DE).

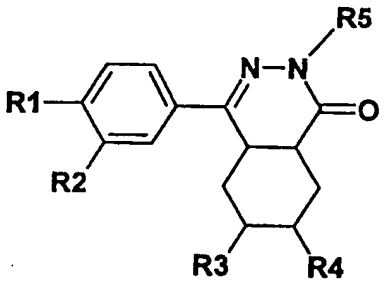
(81) Designated States: AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NEW PHTHALAZINONES

(57) Abstract

Compounds of formula (I) wherein R1, R2, R3, R4 and R5 have the meanings as given in the description are novel effective bronchial–therapeutics.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

New Phthalazinones

Field of application of the invention

The invention relates to novel compounds which are used in the pharmaceutical industry for the production of medicaments.

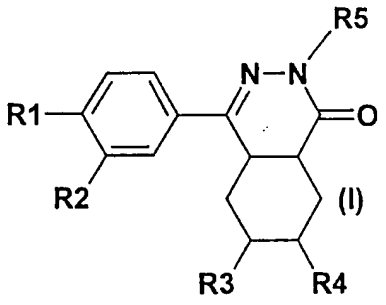
Known technical background

International Patent Applications WO91/12251 and WO93/07146 describe phthalazinones having bronchodilating and antiasthmatic properties. International Patent Application WO94/12461 describes 3-aryl-pyridazin-6-one derivatives as selective PDE4 inhibitors.

Description of the invention

It has been found that the phthalazinones described in greater details below have surprising and particulary advantageous properties.

The invention thus relates to compounds of formula I,



in which

R1 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is hydroxyl or stands for -O-C_rH_{2r}-R21, wherein

R21 is chlorine, bromine, hydroxyl, cyano, carboxyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, pyrazolyl, pyrrolyl, indolyl, isoindolyl, benzimidazolyl, benzotriazolyl, indazolyl, purinyl, a phenyl

radical substituted by R22 and/or R23, a phenoxy radical substituted by R24 and/or R25, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R23 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R24 is hydrogen, hydroxyl, nitro, cyano, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, tetrazolyl, purinyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R25 is hydrogen, hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, nitro or halogen,

R26 is hydrogen, halogen, hydroxyl, nitro, 1-4C-alkyl, 1-4C-alkoxy, carboxy-1-4C-alkyl, carboxyl or 1-4C-alkoxycarbonyl,

R3 and R4 are both hydrogen or together form an additional bond,

R5 is R6 or $-C_pH_{2p}$-Ar, in which

R6 is hydrogen, 1-8C-alkyl, 3-10C-cycloalkyl, 3-7C-cycloalkylmethyl, 7-10C-polycycloalkyl, pyridyl, or an unsubstituted or by R61 and/or R62 substituted phenyl radical, in which

R61 is 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, nitro or halogen, and

R62 is 1-4C-alkyl, nitro or halogen,

Ar is an unsubstituted phenyl, naphthyl or pyridyl radical, or a phenyl radical substituted by R7 and/or R8, in which

R7 is hydroxyl, halogen, nitro, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl, and

R8 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

p is an integer from 1 to 4,

r is an integer from 1 to 8,

and the salts of these compounds.

One embodiment of the invention are compounds of formula I, in which

R1 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is hydroxyl or stands for $-O-C_rH_{2r}$-R21, wherein

R21 is chlorine, bromine, hydroxyl, cyano, carboxyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, pyrazolyl, pyrrolyl, indolyl, isoindolyl, benzimidazolyl, benzotriazolyl, indazolyl, purinyl, a phenyl radical substituted by R22 and/or R23, a phenoxy radical substituted by R24 and/or R25, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R23 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R24 is hydrogen, hydroxyl, nitro, cyano, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, tetrazolyl or purinyl,

R25 is hydrogen, hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, nitro or halogen,

R26 is hydrogen, halogen, hydroxyl, nitro, 1-4C-alkyl, 1-4C-alkoxy, carboxy-1-4C-alkyl, carboxyl or 1-4C-alkoxycarbonyl,

R3 and R4 are both hydrogen or together form an additional bond,

R5 is R6 or $-C_pH_{2p}$-Ar, in which

R6 is hydrogen, 1-8C-alkyl, 3-10C-cycloalkyl, 3-7C-cycloalkylmethyl, 7-10C-polycycloalkyl, pyridyl, or an unsubstituted or by R61 and/or R62 substituted phenyl radical, in which

R61 is 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, nitro or halogen, and

R62 is 1-4C-alkyl, nitro or halogen,

Ar is an unsubstituted phenyl, naphthyl or pyridyl radical, or a phenyl radical substituted by R7 and/or R8, in which

R7 is hydroxyl, halogen, nitro, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl, and

R8 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

p is an integer from 1 to 4,

r is an integer from 1 to 8,

and the salts of these compounds.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical, which, in addition to the oxygen atom contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, iso-butoxy, sec-butoxy, tert-butoxy, propoxy and in particular the isopropoxy, ethoxy and methoxy radicals.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred.

1-4C-Alkoxycarbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples are the methoxycarbonyl [CH_3O-C(O)-] and the ethoxycarbonyl [CH_3CH_2O-C(O)-] radical.

1-4C-Alkylcarbonyloxy stands for a carbonyloxy group to which one of the abovementioned 1-4C-alkyl radicals is bonded. An example is the acetoxy radical [CH_3C(O)-O-].

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Examples, which may be mentioned are the dimethylamino, the diethylamino and the diisopropylamino radical.

An 1-4C-Alkylcarbonylamino radical is, for example, the propionylamino [C_3H_7C(O)NH-] and the acetylamino radical [CH_3C(O)NH-].

Mono- or Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl- the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropylaminocarbonyl radical.

Mono- or Di-1-4C-alkylaminosulfonyl stands for a sulfonyl group to which one of the abovementioned mono- or di-1-4C-alkylamino radicals is bonded. Examples which may be mentioned are the methylaminosulfonyl, the dimethylaminosulfonyl and the ethylaminosulfonyl radical.

Halogen within the meaning of the present invention is bromine, chlorine and fluorine.

Carboxy-1-4C-alkyl radicals are, for example, the carboxymethyl (-CH_2COOH) and the carboxyethyl (-CH_2CH_2COOH) radical.

3-10C-Cycloalkyl radicals are, for example, the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the cyclooctyl radical.

3-7C-Cycloalkylmethyl stands for a methyl radical, which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopropylmethyl, the cyclobutylmethyl and the cyclopentylmethyl radicals.

7-10C-Polycycloalkyl stands for 7-10C-bicycloalkyl or 7-10C-tricycloalkyl groups, such as for example, bornyl, norbornyl or adamantyl.

Possible groups $-C_rH_{2r}-$ and $-C_pH_{2p}-$ are straight chain or branched groups.

Examples which may be mentioned for the $-C_rH_{2r}-$ group are the octylene, heptylene, isoheptylene (2-methylhexylene), hexylene, isohexylene (2-methylpentylene), neohexylene (2,2-dimethylbutylene), pentylene, isopentylene (2-methylbutylene), neopentylene (2,2-dimethylpropylene), butylene, isobutylene, sec-butylene, tert-butylene, propylene, isopropylene, ethylene, 1-methylmethylene and the methylene group.

Examples which may be mentioned for the $-C_pH_{2p}-$ group are the butylene, isobutylene, sec-butylene, tert-butylene, propylene, isopropylene, ethylene, 1-methylmethylene and the methylene group.

From the groups $-O-C_rH_{2r}-R21$ those are preferred in which $-C_rH_{2r}-$ is a straight chain group and r is an integer from 2 to 6.

Aza-heterocycles which are a component (R21) of the group of substituents defined as $-O-C_rH_{2r}-R21$ and contain the grouping -NH- (imino), such as for example, pyrrole, imidazole, benzimidazole, benzotriazole or purine, are preferably bonded via their imino-nitrogen to the $-C_rH_{2r}-$ group.

The term coumarinyloxy preferably stands for coumarinyl-4-oxy or coumarinyl-7-oxy.

Suitable salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts with the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

Compounds of the formula I to be emphasized are those in which

R1 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is hydroxyl or stands for -O-C_rH_{2r}-R21, wherein

R21 is chlorine, bromine, hydroxyl, carboxyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, pyrrolyl, imidazolyl, pyrazolyl, benzimidazolyl, indolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, halogen, carboxyl, carboxy-1-4C-alkyl or 1-4C-alkoxycarbonyl,

R24 is hydrogen, nitro, cyano, halogen, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, tetrazolyl, imidazolyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R26 is hydrogen, hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, carboxyl or carboxy-1-2C-alkyl,

R3 and R4 are both hydrogen or together form an additional bond,

R5 is R6 or -C_pH_{2p}-Ar, in which

R6 is hydrogen, 1-8C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl, bornyl, norbornyl, adamantyl, pyridyl, or an unsubstituted or by R61 substituted phenyl radical, in which

R61 is 1-2C-alkyl, 1-2C-alkoxy, carboxyl, 1-2C-alkoxycarbonyl or halogen,

Ar is an unsubstituted or by R7 substituted phenyl radical, in which

R7 is hydroxyl, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkylcarbonyloxy or 1-4C-alkoxycarbonyl and

p is an integer from 1 to 2,

r is an integer from 1 to 8,

and the salts of these compounds.

One embodiment of the compounds of formula I to be emphasized are those compounds in which

R1 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is hydroxyl or stands for -O-C_rH_{2r}-R21, wherein

R21 is chlorine, bromine, hydroxyl, carboxyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, pyrrolyl, imidazolyl, pyrazolyl, benzimidazolyl, indolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, halogen, carboxyl, carboxy-1-4C-alkyl or 1-4C-alkoxycarbonyl,

R24 is hydrogen, nitro, cyano, halogen, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, tetrazolyl or imidazolyl,

R26 is hydrogen, hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, carboxyl or carboxy-1-2C-alkyl,

R3 and R4 are both hydrogen or together form an additional bond,

R5 is R6 or $-C_pH_{2p}$-Ar, in which

R6 is hydrogen, 1-8C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl, bornyl, norbornyl, adamantyl, pyridyl, or an unsubstituted or by R61 substituted phenyl radical, in which

R61 is 1-2C-alkyl, 1-2C-alkoxy, carboxyl, 1-2C-alkoxycarbonyl or halogen,

Ar is an unsubstituted or by R7 substituted phenyl radical, in which

R7 is hydroxyl, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkylcarbonyloxy or 1-4C-alkoxycarbonyl and

p is an integer from 1 to 2,

r is an integer from 1 to 8,

and the salts of these compounds.

Compounds of the formula I particulary to be emphasized are those in which

R1 is methoxy, ethoxy, difluoromethoxy or trifluoromethoxy,

R2 is hydroxyl or stands for $-O-C_rH_{2r}$-R21, wherein

R21 is chlorine, bromine, hydroxyl, carboxyl, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, pyrrolyl, imidazolyl, pyrazolyl, benzimidazolyl, indolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, carboxyl or carboxy-1-2C-alkyl,

R24 is hydrogen, cyano, carboxyl, carboxy-1-2C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, tetrazolyl, imidazolyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R26 is hydrogen, 1-2C-alkyl or carboxy-1-2C-alkyl,

R3 and R4 form together an additional bond,

R5 is R6 or $-C_pH_{2p}$-Ar, in which

R6 is 3-7C-cycloalkyl or an unsubstituted or by R61 substituted phenyl radical, in which

R61 is carboxyl or 1-2C-alkoxycarbonyl,

Ar is an unsubstituted or by R7 substituted phenyl radical, in which

R7 is carboxyl, carboxy-1-2C-alkyl or 1-2C-alkoxycarbonyl,

p is 1,

r is an integer from 1 to 6,

and the salts of these compounds.

One embodiment of the compounds of formula I particularly to be emphasized are those compounds in which

R1 is methoxy, ethoxy, difluoromethoxy or trifluoromethoxy,

R2 is hydroxyl or stands for $-O-C_rH_{2r}-R21$, wherein

R21 is chlorine, bromine, hydroxyl, carboxyl, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, pyrrolyl, imidazolyl, pyrazolyl, benzimidazolyl, indolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, carboxyl or carboxy-1-2C-alkyl,

R24 is hydrogen, cyano, carboxyl, carboxy-1-2C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, tetrazolyl or imidazolyl,

R26 is hydrogen, 1-2C-alkyl or carboxy-1-2C-alkyl,

R3 and R4 form together an additional bond,

R5 is R6 or $-C_pH_{2p}-Ar$, in which

R6 is 3-7C-cycloalkyl or an unsubstituted or by R61 substituted phenyl radical, in which

R61 is carboxyl or 1-2C-alkoxycarbonyl,

Ar is an unsubstituted or by R7 substituted phenyl radical, in which

R7 is carboxyl, carboxy-1-2C-alkyl or 1-2C-alkoxycarbonyl,

p is 1,

r is an integer from 1 to 6,

and the salts of these compounds.

Preferred compounds of the formula I are those in which

R1 is methoxy,

R2 is hydroxyl or stands for $-O-C_rH_{2r}-R21$, wherein

R21 is bromine, hydroxyl, carboxyl, dimethylamino, imidazolyl, benzimidazolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is carboxymethyl,

R24 is hydrogen, carboxyl, carboxymethyl, aminocarbonyl, cyano, tetrazolyl, imidazolyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R26 is hydrogen, methyl or carboxymethyl,

R3 and R4 form together an additional bond

R5 is 5-7C-cycloalkyl or phenyl,

r is an integer from 1 to 6,

and the salts of these compounds.

One embodiment of the preferred compounds of formula I are those compounds in which

R1 is methoxy,

R2 is hydroxyl or stands for -O-C_rH_{2r}-R21, wherein

R21 is bromine, hydroxyl, carboxyl, dimethylamino, imidazolyl, benzimidazolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is carboxymethyl,

R24 is hydrogen, carboxyl, carboxymethyl, aminocarbonyl, cyano, tetrazolyl or imidazolyl,

R26 is hydrogen, methyl or carboxymethyl,

R3 and R4 form together an additional bond

R5 is 5-7C-cycloalkyl or phenyl,

r is an integer from 1 to 6,

and the salts of these compounds.

Especially preferred compounds of the formula I are those in which

R1 is methoxy,

R2 stands for -O-C_rH_{2r}-R21, wherein

R21 is hydroxyl, imidazolyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is carboxymethyl,

R24 is hydrogen, carboxyl, carboxymethyl, aminocarbonyl, cyano or imidazolyl,

R26 is hydrogen, methyl or carboxymethyl,

R3 and R4 form together an additional bond,

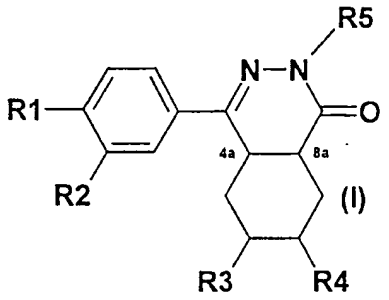
R5 is cyclopentyl, cycloheptyl or phenyl,

r is an integer from 1 to 6,

and the salts of these compounds.

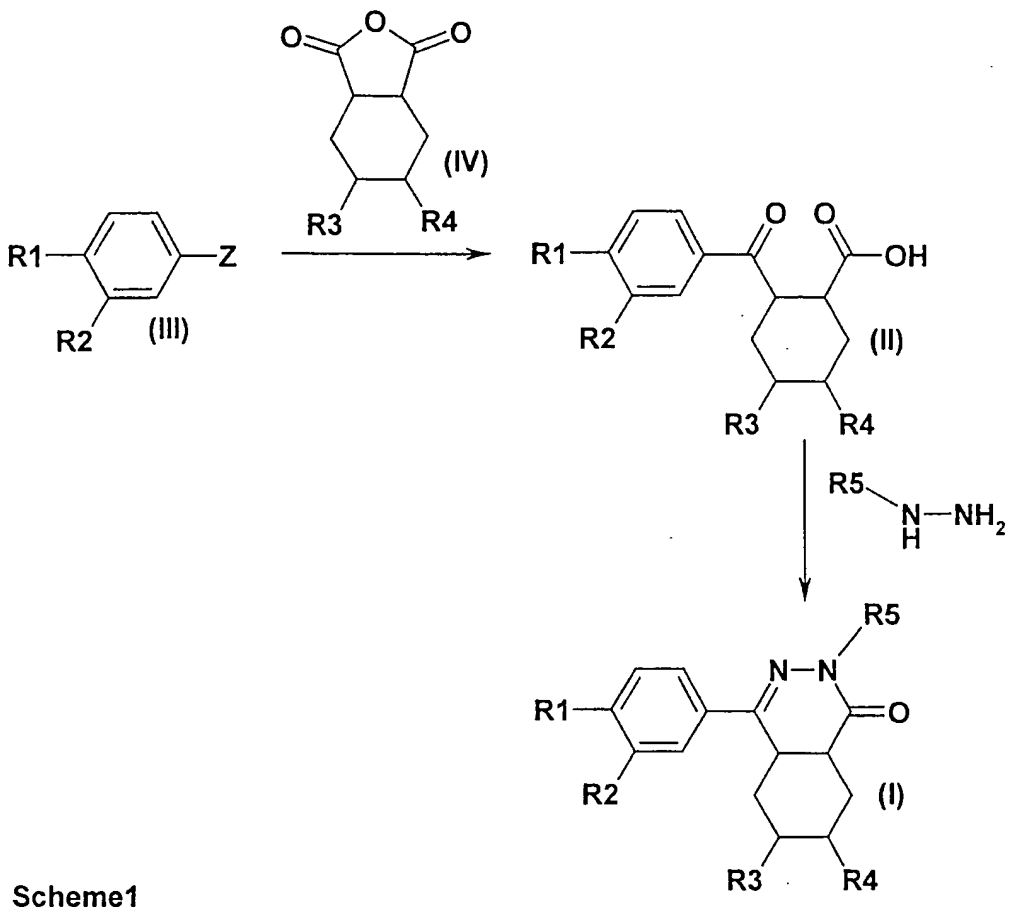
The compounds of formula I are chiral compounds with chiral centers in the positions 4a and 8a.

Numbering:



Therefore the invention includes all conceivable pure diastereomers and pure enantiomers, as well as all mixtures thereof independent from the ratio, including the racemates. Preferred are those compounds, in which the hydrogen atoms in the positions 4a and 8a are cis-configurated. Especially preferred are in this connection those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a. Racemates can be split up into the corresponding enantiomers by methods known by a person skilled in the art. Preferably the racemic mixtures are separated into two diastereomers with the help of an optical active separation agent on the stage of the cyclohexanecarboxylic acids (for example, starting compound B1) or the 1,2,3,6-tetrahydrobenzoic acids (for example, starting compound A1). As separation agents may be mentioned, for example, optical active amines such as the (+)- and (-)-forms of α-phenylethylamin and ephedrine, or the optical active alkaloids cinchonine, cinchonidine and brucine.

The preparation of compounds of formula I can be performed, for example, as described in the following reaction schemes:



Scheme1

In scheme 1, the Keto acids of formula II, in which R1, R2, R3 and R4 have the abovementioned meanings can, for example, be prepared from compounds of the formula III, in which R1 and R2 have the abovementioned meanings and Z represents hydrogen (H) by a Friedel-Crafts acylation with compounds of the formula IV, in which R3 and R4 have the abovementioned meanings.

The Friedel-Crafts acylation is carried out in a manner which in known by the skilled person (for example as described in M. Yamaguchi et al., J. Med. Chem. 36: 4052-4060, 1993) in presence of a suitable catalyst, such as for example, $AlCl_3$, $ZnCl_2$, $FeCl_3$ or iodine, in an appropriate inert solvent, such as methylene chloride or nitrobenzene or another inert solvent such as diethylether, preferably at raised temperature, especially at the boiling point of the solvent being used.

Alternatively, the compounds of formula II, in which R1, R2, R3 and R4 have the abovementioned meanings, can be prepared from compounds of the formula III, in which R1 and R2 have the above-mentioned meanings and Z represents a halogen atom through reaction with compounds of the formula IV, in which R3 and R4 have the abovementioned meanings.

The reaction is carried out in a manner which is known by a person skilled in the art, for example

a) by activating compounds of formula III, in which R1, R2 and Z have the abovementioned meanings, by a lithium/halogen exchange reaction at low temperatures (preferably at -60 to -100°C) in an appropriate inert solvent such as tetrahydrofuran or diethylether, preferably under an atmosphere of inert gas, followed by reaction of the lithiated compounds with cyclic carboxylic acid anhydrides of formula IV, or

b) by converting compounds of formula III in which R1, R2 and Z have the abovementioned meanings, in a suitable inert solvent such as, for example, tetrahydrofuran or diethylether into the corresponding Grignard compounds of formula III in which Z represents MgCl, MgBr or MgI followed by reaction of the Grignard compounds with cyclic carboxylic acid anhydrides of formula IV, in which R3 and R4 have the abovementioned meanings.

Compounds of formula III, in which R1 and R2 have the abovementioned meanings and Z represents a hydrogen (H) or halogen atom, are known or can be prepared by methods known by a person skilled in the art.

Compounds of formula IV, in which R3 and R4 have the abovementioned meanings are as well known or can be prepared by methods known by a person skilled in the art.

The compounds of formula I can be prepared by

a) reacting keto acids of formula II or one of their reactive derivatives in which R1, R2, R3 and R4 have the abovementioned meanings in a first step with hydrazine hydrate to compounds of formula I in which R1, R2, R3 and R4 have the abovementioned meanings and R5 stands for hydrogen (H).

   If desired, these compounds can be further reacted with alkylating agents of formula R5-X, in which R5 has the abovementioned meanings [exception: R5 does not represent hydrogen (H)] and X represents a leaving group to give further compounds of formula I, in which R1, R2, R3, R4 and R5 have the abovementioned meanings [exception: R5 does not represent hydrogen (H)].

b) reacting, alternatively to procedure a), keto acids of formula II or one of their reactive derivatives, in which R1, R2, R3 and R4 have the abovementioned meanings with suitable hydrazine derivates of formula R5-NH-NH_2, in which R5 has the abovementioned meanings [exception: R5 does not represent hydrogen (H)], to give compounds of the formula I, in which R1, R2, R3, R4 and R5 have the abovementioned meanings [exception: R5 does not represent hydrogen (H)].

The conversion of the keto acids of formula II or one of their reactive derivatives with hydrazine hydrate [according to procedure a)] respectively with suitable hydrazine-derivates of the formula R5-NH-NH_2 [according to procedure b)] is advantageously carried out with one to five equivalents of hydrazine hydrate respectively the suitable hydrazine derivates of formula R5-NH-NH_2, which simultaneously can be used as solvent. More suitable is, however, to use an additional appropriate solvent. As inert solvents are preferably used alcohols such as methanol, ethanol, isopropanol, n-butanol, isoamylalcohol, glycols and their ethers such as ethylene glycol, diethylene glycol, ethylene glycol monomethyl or monoethyl ether, carboxylic acids such as formic acid, acetic or propionic acid, suitable mixtures of the abovementioned solvents, as well as mixtures with water, for example aqueous ethanol, further ethers, especially water soluble ethers such as tetrahydrofuran, dioxane or ethylene glycol dimethylether; further toluene or benzene, especially when the method of azeotropic destillation is used to remove the reaction water.

The reaction temperatures are suitably between 0 and 200°C, preferably between 20 and 100°C; the reaction times are preferably between 1 and 48 hours.

Suitable reactive derivatives of the keto acids of formula II which may be mentioned in this context are, for example, esters, especially methyl and ethyl esters, nitrils and acid halides, such as acid chlorides or acid bromides. They can be prepared, for example, starting from the corresponding keto acids of formula II, by methods which are known by the person skilled in the art.

The conversion of compounds of formula I, in which R1, R2, R3 and R4 have the abovementioned meanings and R5 represents hydrogen (H) with alkylating agents of the formula R5-X, in which R5 has the abovementioned meanings [with the exception of hydrogen(H)] and X represents a suitable leaving group, is carried out in a manner, which is known by a person skilled in the art.

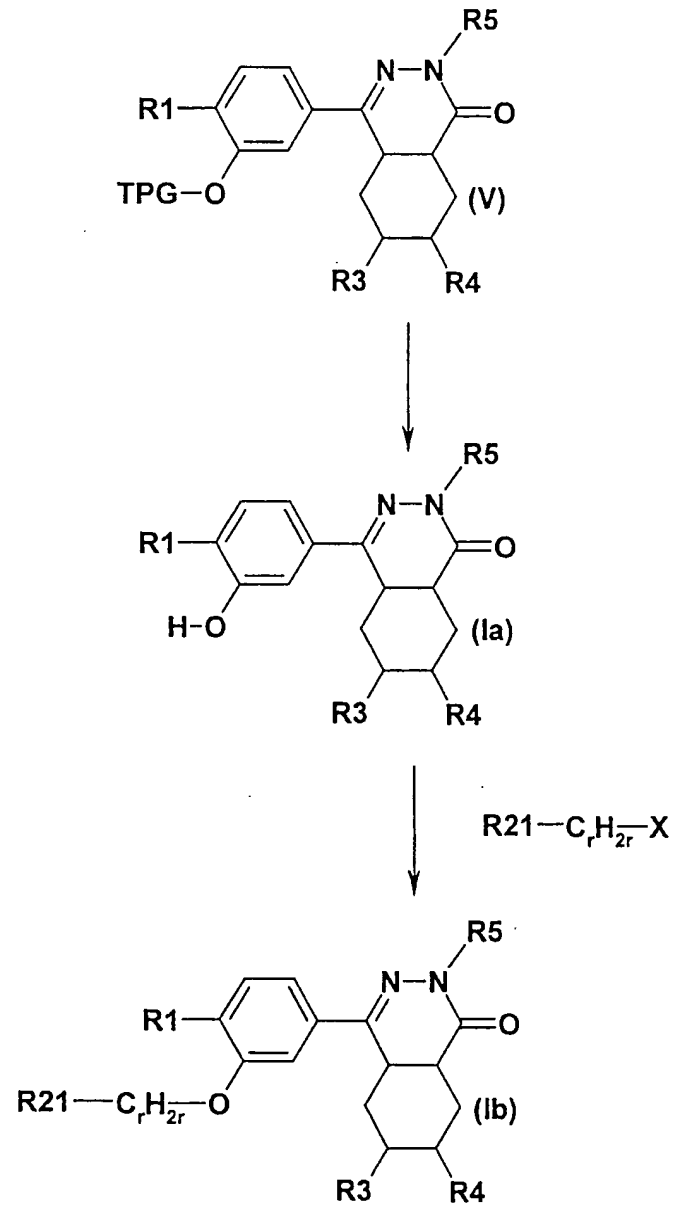
In a first step, the hydrogen atom (H) of the NH-group of the compounds of formula I, in which R5 represents a hydrogen atom (H) is removed by a base such as, for example, potassium carbonate, sodium hydroxide, sodium hydride, sodium methanolate, sodium ethanolate or buthyllithium in a suitable inert solvent such as dimethylformamide, dimethylsulfoxide, tetrahydrofuran or diethylether. The alkylation is then carried out by adding an appropriate alkylating agent of the formula R5-X.

The bases are preferably used in more than an equimolar ratio; the reaction temperature is preferably between 0 and 150°C.

Examples of suitable leaving groups X which may be mentioned are halogen atoms, especially chlorine, or hydroxyl groups activated by esterification (for example with p-toluenesulfonic acid).

For some compounds according to the invention it is preferable to assemble the final meaning of the substituent R2 only in a late stage of the synthesis.

In these cases the synthetic pathway of scheme 1 is slightly modified as shown in scheme 2:



Scheme 2

In scheme 2, the compounds of formula I, in which R1, R3, R4 and R5 have the abovementioned meanings and R2 represents -O-TPG, hydroxyl or -O-C_rH_{2r}-R21 are shown as formula V (R2 = -O-TPG), formula Ia (R2 = hydroxyl) and formula Ib (R2 = -O-C_rH_{2r}-R21).

The compounds of formula V, in which R1, R3, R4 and R5 have the abovementioned meanings and R2 represents -O-TPG, wherein TPG stands for a suitable temporary protective group can be prepared analogously to the compounds of formula I following the reaction pathway of scheme 1.

As suitable temporary protection groups in this connection may be mentioned, for example, the 2-tetrahydropyranyl, t-butyl, isopropyl, allyl, benzyloxymethyl, methoxyethoxyethyl, methylthiomethyl, methoxymethyl, cyclopropylmethyl, cyclopentyl and the cyclohexyl group.

The compounds of formula Ia can be obtained starting from the compounds of formula V through a selective ether cleavage reaction.

These ether cleavage reactions are carried out in a manner which is known by the person skilled in the art (for example as described in Th. Greene, Protective Groups in organic synthesis, Chapter 3, John Wiley & Sons, 1991).

In those cases, where the cyclopentyl group is used as temporary protective group, the ether cleavage reaction can be performed, for example, using a strong acid like sulphuric acid, hydrochloric acid or p-toluenesulphonic acid, in an inert solvent, such as for example, benzene or toluene, preferably at raised temperature, especially at the boiling temperature of the solvent being used.

The alkylation of the compounds of formula Ia with compounds of formula $X\text{-}C_rH_{2r}\text{-}R21$, in which r and R21 have the abovementioned meanings and X represents a suitable leaving group, for example a halogen atom, preferably a bromine atom, or a hydroxyl group activated by esterification (for example with p-toluenesulphonic acid) then yields the compounds of formula Ib.

The alkylation reactions are carried out using standard conditions which are familiar to the person skilled in the art.

Additionally, it is possible to convert one functional group of a compound of formula I (Ib) to another functional group by customary methods and reactions.

Thus, if desired, compounds of formula I (Ib) with suitable functional groups can be converted into further compounds of formula I.

For instance, compounds of formula I (Ib), in which R21 comprises an ester can be converted by acidic or alkaline saponification to the corresponding carboxylic acid or by reaction with a suitable amine to the corresponding amide.

Furthermore, compounds of formula I (Ib), in which R21 comprises a reactive leaving group such as, for example, a halogen atom, can be converted to the corresponding amines by reaction with an appropriate amine.

Suitably, the conversions are carried out analogous to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described in the following examples.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent, e.g. in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol (ethanol, isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification or by acidifying into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula I, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods. The compounds, which are mentioned in the examples as well as their salts are preferred compounds of the invention.

Examples

Final Products

1. (cis)-4-(3-Hydroxy-4-methoxyphenyl)-2-cyclopentyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A solution of 3.3 g of compound C and 2 g of p-toluenesulphonic acid in 15 ml of toluene was refluxed for 4 hours in a Dean-Stark apparatus. After cooling to room temperature, the mixture was washed with aqueous sodium carbonate, the toluene solution was dried over magnesium sulfate and evaporated. Crystallized from diethyl ether/petroleum ether (60-80°C). M.p. 142-144°C

2. (cis)-4-(3-Hydroxy-4-methoxyphenyl)-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from compound D and p-toluenesulphonic acid in a Dean-Stark apparatus as described for compound 1. M.p. 171°C

3. (cis)-4-(3-Hydroxy-4-methoxyphenyl)-2-cycloheptyl-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-one

Prepared from compound F and p-toluenesulphonic acid in a Dean-Stark apparatus as described for compound 1. M.p. 120-122°C

4. (cis)-4-(3-Hydroxy-4-methoxyphenyl)-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from compound E and p-toluenesulphonic acid in a Dean-Stark apparatus as described for compound 1. Crystallized from diethyl ether. M.p. 146-149°C

5. (cis)-2-[5-(2-Cycloheptyl-1-oxo-1,2,4a,5,8,8a-hexahydro-phthalazin-4-yl)-2-methoxyphenoxy]-acetic acid

A mixture of 1 g of compound 2, 0.5 g of ethyl bromoacetate and 0.4 g of potassium carbonate in N-Methyl-2-pyrrolidinone was stirred at 60°C for 6 hours. After cooling to room temperature and addition of diethyl ether, the mixture was washed with water. After evaporating the solvent, the residue was dissolved in a mixture of tetrahydrofuran (100 ml), methanol (100 ml) and 200 ml of 2 M potassium hydroxide. After stirring for 2 hours the organic solvents were evaporated and the residue was washed with ethyl acetate. The waterlayer was acidified with hydrochloric acid and extracted with ethyl acetate.

After drying over magnesium sulfate and evaporating the solvent, the compound was crystallized from diethyl ether. M.p. 143°C

6. (cis)-4-[5-(2-Cycloheptyl-1-oxo-1,2,4a,5,8,8a-hexahydro-phthalazin-4-yl)-2-methoxy-phenoxy]-butyric acid

Prepared from compound 2 and ethyl 4-bromobutyrate as described for compound 4. Crystallized from diethyl ether. M.p. 121°C

7. (cis)-5-[5-(2-Cycloheptyl-1-oxo-1,2,4a,5,8,8a-hexahydro-phthalazin-4-yl)-2-methoxy-phenoxy]-valeric acid

Prepared from compound 2 and ethyl 5-bromovalerate as described for compound 4. Crystallized from ethyl acetate. M.p. 161°C

8. (cis)-2-Cycloheptyl-4-(3-hydroxyethoxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 1g of compound 3, 0.5 g of ethylenecarbonate and 0.8 g of K_2CO_3 was stirred at 125°C in 1-methyl-2-pyrrolidinone (20 ml) for 4 hours. The reaction was diluted with water (100 ml) and the resulting mixture extracted with ether. After drying over magnesium sulfate and evaporating, the compound was purified by chromatography [petroleum ether (60-80°C):ethyl acetate/1:1] Crystallisation from ether/petroleum ether (60-80°C). M.p. 75°C

9. (cis)-4-[3-(2-Bromoethoxy)-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from 4 g of compound 2, 7.5 g of 1,2-dibromoethane and 2.7 g of potassium carbonate as described for compound 11.

Alternative preparation: A solution of 25 mmol of bromine in 10 ml of dichloromethane was added to a solution of 25 mmol of triphenylphosphine in 50 ml of dichloromethane at 0°C under a flow of nitrogen, followed by the addition of 25 mmol of compound 8 in 25 ml of dichloromethane. After complete addition, the mixture was stirred for 2 hours at room temperature. The reaction mixture was washed with aqueous sodium carbonate, dried over magnesium sulfate and evaporated. Crystallized from methanol. M.p 92-94°C

10. **(cis)-4-[3-(4-Bromo-1-butoxy)-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from 4 g of compound 2, 7.5 g 1,4-dibromobutane and 2.7 g of potassium carbonate in N-methyl-2-pyrrolidinone as described for compound 11. M.p. 101-103°C

11. **(cis)-4-[3-(4-Bromobutoxy)-4-methoxyphenyl]-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A mixture of 6 g of compound 4, 13 g of 1,4-dibromobutane and 2.8 g of K_2CO_3 was stirred in 1-methyl-2-pyrrolidinone (100 ml) for 4 hours at 60 °C. Then the mixture was diluted with water (300 ml) and extracted with diethyl ether. The ether layer was dried over magnesium sulfate and evaporated. Purified by chromatography (petroleum ether (60-80°C)/ethyl acetate, 4:1). Yield: 80%. M.p oil.

^{1}H-NMR:($CDCl_3$): 1.92-2.40 (m, 7 H,3 x cyclopentyl-H, O-C-CH_2-CH_2); 2.95-3.15 (m, 2 H,2 x cyclohexene-H); 3.42-3.60 (m, 3 H, cyclohexene-H, CH_2Br); 3.89 (s, 3 H, OCH_3); 4.03-4.13 (m, 2 H, OCH_2); 5.63-5.89 (m, 2 H, CH=CH); 6.89 (d, J=8.8Hz, 2 H, Ar-H); 7.21-7.63 (m, 7 H, Ar-H);

12. **(cis)-4-[3-(6-Bromo-1-hexyloxy)-4-methoxyphenyl]-2-cyclopentyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A mixture of 2 g of compound 1, 4.3 g of 1,6-dibromohexane and 1.1 g potassium carbonate was stirred in dimethylformamide at 60°C for 2 hours. After evaporating the solvent, the residue was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate, evaporated and the residue was purified by column chromatography [petroleum ether (60-80°C): ethyl acetate / 7:1].

^{1}H-NMR ($CDCl_3$): 1.41-2.29 (m, 8 H, cyclopentyl, 3 H, cyclohexene, 8 H, hexyl), 2.65-2.75 (m, 1 H, cyclohexene), 2.90-3.10 (m, 1 H, cyclohexene), 3.25-3.40 (m, 1 H, cyclohexene), 3.43 (t, J=6.8 Hz, 2 H, CH_2-Br), 3.90 (s, 3 H, OCH_3), 4.08 (t, J=6.7 Hz, 2 H, O-CH_2), 5.15-5.32 (m, 1 H, cyclopentyl), 5.61-5.88 (m, 2 H, CH=CH), 6.87 (d, J=8.5 Hz, 1 H, phenyl), 7.13-7.31 (m, 1 H, phenyl), 7.50 (d, J=2.0 Hz, 1 H, phenyl).

13. **(cis)-4-[3-(6-Bromo-1-hexyloxy)-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from compound 2 and 1,6-dibromohexane as described for compound 12. M.p. 104-105°C

14. (cis)-4-[3-{2-(N,N-Dimethylamino)-ethoxy}-4-methoxyphenyl]-2-cycloheptyl-4a,5,6,8a-tetrahydro-2H-phthalazin-1-one hemifumarate

Prepared from compound 9 as described for compound 16. M.p. 163°C

15. (cis)-4-[3-{4-(N,N-Dimethylamino)butoxy}-4-methoxyphenyl]-2-cycloheptyl-4a,5,6,8a-tetrahydro-2H-phthalazin-1-one hemifumarate

Prepared from compound 10 as described for compound 16. The titel compound was precipitated as the hemifumarate from ethyl acetate by the addition of a saturated solution of fumaric acid in diethyl ether. M.p. 146°C

16. (cis)-4-[3-{6-(N,N-Dimethylamino)-1-hexyloxy}-4-methoxyphenyl]-2-cyclopentyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

0.7 g of compound 12 were stirred for 5 hours in a solution of 30 ml of a 20 % solution of dimethylamine in ethanol. After evaporating the mixture, the residue was partitioned between aqueous sodium carbonate and ethyl acetate. The ethyl acetate solution was dried over magnesium sulfate and evaporated. The residue was crystallized from a mixture of diethyl ether and petroleum ether (60-80°C). M.p. 68-69°C

17. (cis)-4-[3-{4-(1-Imidazoyl)-1-butoxy}-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

Prepared from compound 10 as described for compound 18. Precipitated as the hydrochloride from ethyl acetate by the addition of a solution of hydrochloric acid in diethyl ether. M.p. 73-74°C

18. (cis)-4-[3-{6-(1-Imidazoyl)-1-hexyloxy}-4-methoxyphenyl]-2-cyclopentyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

A mixture of 0.7 g of compound 12, 0.2 g of imidazole and 0.3 g of potassium carbonate in 25 ml N-methyl-2-pyrrolidinone was stirred at 70°C for 1 hour. After dilution with ethyl acetate, the mixture was washed with aqueous sodium carbonate. The organic layer was dried over magnesium sulfate and addition of a solution of hydrochloric acid in ether caused precipitation of the compound as the hydrochloride. M.p. 123°C.

19. (cis)-4-[3-(4-Carboxymethyl)phenylmethoxy-4-methoxyphenyl)-2-cyclopentyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 1.0 g of compound 1, 1.1 g of potassium carbonate and 0.9 g of 4-(bromomethyl)benzoic acid was stirred in N-methyl-2-pyrrolidinone for 12 hours at 70°C. After dilution with ethyl acetate, the mixture was extracted with aqueous sodium carbonate. The water layer was acidified and extracted with dichloromethane. After evaporating the solvent, the residue was crystallized from diethyl ether. M.p. 92-94°C

20. (cis)-4-[4-{5-(2-Cycloheptyl-1-oxo-1,2,4a,5,8,8a-hexahydro-phthalazin-4-yl)-2-methoxyphenoxy}-butoxy]-benzoic acid

Prepared from compound 10 and ethyl 4-hydroxy benzoate as described for compound 5. Crystallized from diethyl ether. M.p. 142-143°C

21. (cis)-4-[3-{4-(4-Carboxyphenoxy)-1-butoxy}-4-methoxyphenyl]-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 1 g of compound 11, 0.3 g of ethyl 4-hydroxybenzoate and 0.5 g of K_2CO_3 was stirred in 1-methyl-2-pyrrolidinone (20 ml) at 60 °C for 6 hours. Then the mixture was diluted with water (100 ml) and extracted with diethyl ether. The ether layer was dried over magnesium sulfate and evaporated. The residue after evaporating was stirred in a mixture of 2N KOH (50 ml), methanol (50 ml) and tetrahydrofuran (50 ml) for 2 hours. The organic solvents were evaporated and the residue acidified with hydrochloric acid. After extraction with ethyl acetate the compound was purified by chromatography [petroleum ether (60-80°C):ethyl acetate:acetic acid/2:1:0.1]. Crystallization from ethyl acetate/diethyl ether. M.p. 148.5°C

22. (cis)-4-[3-{6-(4-Carboxyphenoxy)-1-hexyloxy}-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from compound 12, ethyl 4-hydroxybenzoate as described for compound 21. Crystallized from ether. M p. 141-142°C

23. **(cis)-4-[3-{4-(2-Carboxyphenoxy)-1-butoxy}-4-methoxyphenyl]-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from compound 11 and ethyl 2-hydroxybenzoate as described for compound 20. Purified by chromatography [petroleum ether (60-80°C):ethyl acetate:acetic acid/2:1:0.1]. Crystallized from ethyl acetate/diethyl ether. M.p. 97-99°C.

24. **(cis)-4-[3-{6-(4-Amidophenoxy)-1-hexyloxy)-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from compound 13 and 4-hydroxybenzamide as described for compound 33. Crystallized from ethyl acetate/petroleum ether (60-80°C). M.p. 124-125°C

25. **(cis)-4-[4-Methoxy-3-(4-phenoxy-1-butoxy)phenyl]-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from compound 11 and phenol as described for compound 33. Crystallized from diethyl ether. M.p. 90-92°C

26. **(cis)-4-[3-{4-(4-Cyanophenoxy)-1-butoxy}-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from compound 10 and 4-hydroxybenzonitril as described for compound 33. Crystallized from methanol. M.p. 131-133°C

27. **(cis)-2-Cycloheptyl-4-(4-methoxy-3-[4-{4-(4-tetrazolyl)phenoxy}-1-butoxy]phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A solution of 1.5 g of compound 26, 1.1 g of NaN_3 and 0.9 g of NH_4Cl in 50 ml of DMF was heated for 10 hours at 120°C. After cooling to room temperature, the mixture was evaporated and the residue partitioned between diluted hydrochloric acid and ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by chromatography (ethyl acetate) and the compound crystallized from ethyl acetate. M.p. 153-155°C

28. (cis)-2-Cycloheptyl-4-(3-[4-{4-(1-imidazolyl)phenoxy}-1-butoxy]-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

Prepared from compound 10 and 4-(imidazol-1-yl)phenol as described for compound 33. Purified by chromatography (ethyl acetate). Crystallized from ethyl acetate/dichloromethane as the hydrochloride. M.p. 146-149 °C

29. (cis)-4-[3-{2-(Benzimidazol-1-yl)ethoxy}-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from benzimidazole and compound 9 as described for compound 33. Crystallized from ethyl acetate/petroleum ether (60-80°C). M.p. 121-122°C

30. (cis)-2-Cycloheptyl-4-[4-methoxy-3-{4-(purin-7-yl)-1-butoxy}phenyl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from compound 10 and purine as described for compound 33. Purified by chromatography (ethyl acetate:methanol/3:1). Crystallized from methanol at -20°C. M.p. 110-111°C

31. (cis)-2-Cycloheptyl-4-[4-methoxy-3-{4-(4-methylcoumarin-7-yloxy)-1-butoxy}phenyl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from 7-hydroxy-4-methyl coumarine and compound 11 as described for compound 33. Purification by chromatography [petroleum ether (60-80°C):ethyl acetate/2:1]. Crystallization from ethyl acetate/petroleum ether (60-80°C). M.p. 143-144°C

32. (cis)-4-[3-{6-(Coumarin-4-yloxy)-1-hexyloxy}-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from compound 13 and 4-hydroxycoumarine as described for compound 33. Purified by chromatography [petroleum ether (60-80°C):ethyl acetate/2:1] and crystallized from diethyl ether. M.p. 90-92°C

33. (cis)-4-[4-Methoxy-3-{4-(4-methylcoumarin-7-yloxy)-1-butoxy}phenyl]-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 1 g of compound 11, 1 g of 7-hydroxy-4-methyl coumarine and 2 g of potassium carbonate in 50 ml of 1-methyl-2-pyrrolidinone was heated for 2 hours at 80°C. After dilution with 200 ml of water,

this mixture was extracted with diethyl ether. The ether solution was dried over magnesium sulfate and evaporated. The compound was crystallized from dichloromethane/petroleum ether (60-80°C). M.p. 141-142°C

34. (cis)-4-[3-{4-(4-Carboxymethylcoumarin-7-yloxy)-1-butoxy)-4-methoxyphenyl]-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from compound 11 and ethyl 7-hydroxy-4-coumarinylacetate as described for compound 21. Purified by chromatography [petroleum ether (60-80°C):ethyl acetate:acetic acid/2:1:0.1]. Crystallized from diethyl ether. M.p. 92-95°C

35. (cis)-4-(4-Methoxy-3-[6-{4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)phenoxy}-1-hexyloxy]phenyl)-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 5 mmol of compound 13, 5 mmol of 3-(4-hydroxyphenyl)-4-methyl-1,4,5,6-tetrahydro-pyridazin-6-one and 15 mmol of potassium carbonate in 50 ml of dimethylformamide was heated for 4 h at 110°C. After cooling to room temperature the mixture was partioned between water and diethyl ether. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by chromatography [petroleum ether (60-80°C):ethyl acetate/ 1:1]. Crystallized from 2-propanol. M. p. 124-126°C

Starting compounds

A. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Compound A1 was dissolved in ethanol and the solution was refluxed for 6 hours in the presence of 0.2 mole of hydrazine hydrate. After cooling to room temperature, the precipitate was filtered off and dried. M.p. 166-168°C

A1. (cis)-2-(3-Cyclopentoxy-4-methoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid

A solution of 100 mmol of 1-bromo-3-cyclopentyloxy-4-methoxybenzene in tetrahydrofuran was added slowly to a mixture of 1.1 equivalents of magnesium. After complete addition, the mixture was refluxed for 5 hours and left at room temperature for an additional 18 hours. This mixture was added slowly to a solution of (cis)-1,2,3,6-tetrahydrophthalic anhydride in tetrahydrofuran at 0°C. After complete addition the mixture was refluxed for 6 hours and left at room temperature for an additional 18 hours after which the reaction was quenched with ammonium chloride and the solvent removed under reduced pressure.

The residue was acidified with concentrated hydrochloric acid and the mixture extracted with diethyl ether. The organic layer was dried over magnesium sulfate and evaporated. The residue was dissolved in dichloromethane and the solution filtered over silica. Evaporation of the solvent yielded the title compound which was used in the next step without further purification.

B. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-one

Prepared from compound B1 and hydrazine hydrate as described for compound A. M.p. 175-176°C

B1. 2-(3-Cyclopentyloxy-4-methoxybenzoyl)-cis-cyclohexane-carboxylic acid

Prepared from 1-bromo-3-cyclopentyloxy-4-methoxybenzene and cis-1,2-cyclohexanedicarboxylic anhydride as described for compound A1.

C. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-cyclopentyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 1.5 g of compound A and 0.5 g of a 60 % dispersion of sodium hydride in mineral oil in N-methyl-2-pyrrolidinone was stirred for 1 hour, after which 1.9 g of cyclopentylbromide was added. 1 hour after complete addition, water and diethyl ether was added to the reaction mixture. The ether phase was dried over magnesium sulfate and concentrated under reduced pressure after which the compound crystallized. M.p. 144-145°C

D. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-cycloheptyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from compound A and cycloheptylbromide as described for compound C. Crystallized from petroleum ether (60-80°C). M.p. 106°C

E. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A solution of 2 g of compound A1 and 2.8 g of phenyl hydrazine in a mixture of 100 ml of 1-propanol and 5 ml of triethylamine was refluxed for 18 h. After evaporating the solvent, the residue was partitioned between aqueous and ethyl acetate. The compound was crystallized from methanol. M.p. 134-135°C

F. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-cycloheptyl-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-one

Prepared from compound B and cycloheptylbromide as described for compound C. Crystalized from petroleum ether (60-80°C). M. p. 111-112°C

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral

senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease or multiinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to medicaments for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterase of type 4 (PDE4), ameliorating the symptoms of an PDE4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula I according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries, e.g. in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95%.

The person skilled in the art is familiar with auxiliaries which are suitable for the desired pharmaceutical formulations on account of his expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters, can be used.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation. To do this, these are either administered directly as a powder (preferably in micronized form) or by atomizing solutions or suspensions which contain them. With respect to the preparations and administration forms, reference is made, for example, to the details in European Patent 163 965.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those medicaments which are suitable for topical application. For the production of the medicaments, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The medicaments according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarly between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

In the investigation of PDE 4 inhibition on the cellular plane, the activation of inflammatory cells is ascribed particular importance. An example is FMLP (N-formyl-methionyl-leucyl-phenylalanine)-induced superoxide production of neutrophilic granulocytes, which can be measured as luminol-amplified chemiluminescence. (Mc Phail LC, Strum SL, Leone PA and Sozzani S, The neutrophil respiratory burst mechanism. In "Immunology Series" 57: 47-76, 1992; ed. Coffey RG (Marcel Decker, Inc., New York-Basel-Hong Kong)).

Substances which inhibit chemiluminescence and cytokine secretion and the secretion of proinflammatory mediators on inflammatory cells, in particular neutrophilic and eosinophilic granulocytes, T-lymphocytes, monocytes and macrophages are those which inhibit PDE 4. This isoenzyme of the phosphodiesterase families is particularly represented in granulocytes. Its inhibition leads to an increase in the intracellular cyclic AMP concentration and thus to the inhibition of cellular activation. PDE 4 inhibition by the substances according to the invention is thus a central indicator for the suppression of inflammatory processes. (Giembycz MA, Could isoenzyme-selective phosphodiesterase inhibitors render bronchodilatory therapy redundant in the treatment of bronchial asthma?. Biochem Pharmacol 43: 2041-2051, 1992; Torphy TJ et al., Phosphodiesterase inhibitors: new opportunities for treatment of asthma. Thorax 46: 512-523, 1991; Schudt C et al., Zardaverine: a cyclic AMP PDE 3/4 inhibitor. In "New Drugs for Asthma Therapy", 379-402, Birkhäuser Verlag Basel 1991; Schudt C et al., Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca; Naunyn-Schmiedebergs Arch Pharmacol 344; 682-690, 1991; Tenor H and Schudt C, Analysis of PDE isoenzyme profiles in cells and tissues by pharmacological methods. In „Phosphodiesterase Inhibitors", 21-40, „The Handbook of Immunopharmacology", Academic Press, 1996; Hatzelmann A et al., Enzymatic and functional aspects of dual-selective PDE3/4-Inhibitors. In „Phosphodiesterase Inhibitors", 147-160, „The Handbook of Immunopharmacology", Academic Press, 1996.

Inhibition of PDE 4 activity

Methodology

The activity test was carried out according to the method of Bauer and Schwabe, which was adapted to microtitre plates (Naunyn-Schmiederberg's Arch. Pharmacol. 311, 193-198, 1980). In this test, the PDE reaction is carried out in the first step. In a second step, the resultant 5'-nucleotide is cleaved to the uncharged nucleoside by a snake venom 5'-nucleotidase from Crotalus Atrox. In the third step, the nucleoside is separated from the remaining charged substrate on ion exchange columns. The columns are eluted directly into minivials using 2 ml of 30 mM ammonium formate (pH 6.0), to which a further 2 ml of scintillation fluid is added for counting.

The inhibitory values determined for the compounds according to the invention follow from the following table A, in which the numbers of the compounds correspond to the numbers of the examples.

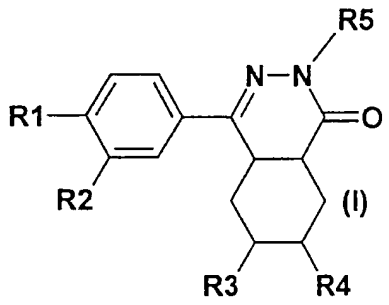
Table A

Inhibition of PDE4 acitivity [measured as -logIC_{50} (mol/l)]

compound	-logIC_{50}
2	7.43
7	7.76
8	8.43
17	8.10
18	8.66
20	9.52
22	8.73
24	9.50
25	8.53
26	8.58
28	9.65
31	9.17
32	8.67
33	8.82
34	9.06

Patent claims

1. Compounds of the formula I,



in which

R1 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is hydroxyl or stands for -O-C_rH_{2r}-R21, wherein

R21 is chlorine, bromine, hydroxyl, cyano, carboxyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, pyrazolyl, pyrrolyl, indolyl, isoindolyl, benzimidazolyl, benzotriazolyl, indazolyl, purinyl, a phenyl radical substituted by R22 and/or R23, a phenoxy radical substituted by R24 and/or R25, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R23 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R24 is hydrogen, hydroxyl, nitro, cyano, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, tetrazolyl, purinyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R25 is hydrogen, hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, nitro or halogen,

R26 is hydrogen, halogen, hydroxyl, nitro, 1-4C-alkyl, 1-4C-alkoxy, carboxy-1-4C-alkyl, carboxyl or 1-4C-alkoxycarbonyl,

R3 and R4 are both hydrogen or together form an additional bond,

R5 is R6 or -C_pH_{2p}-Ar, in which

R6 is hydrogen, 1-8C-alkyl, 3-10C-cycloalkyl, 3-7C-cycloalkylmethyl, 7-10C-polycycloalkyl, pyridyl, or an unsubstituted or by R61 and/or R62 substituted phenyl radical, in which

R61 is 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, nitro or halogen, and

R62 is 1-4C-alkyl, nitro or halogen,

Ar is an unsubstituted phenyl, naphthyl or pyridyl radical, or a phenyl radical substituted by R7 and/or R8, in which

R7 is hydroxyl, halogen, nitro, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl, and

R8 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

p is an integer from 1 to 4,

r is an integer from 1 to 8,

and the salts of these compounds.

2. Compounds of the formula I according to claim 1, in which

R1 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is hydroxyl or stands for $-O-C_rH_{2r}-R21$, wherein

R21 is chlorine, bromine, hydroxyl, cyano, carboxyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, pyrazolyl, pyrrolyl, indolyl, isoindolyl, benzimidazolyl, benzotriazolyl, indazolyl, purinyl, a phenyl radical substitued by R22 and/or R23, a phenoxy radical substituted by R24 and/or R25, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R23 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R24 is hydrogen, hydroxyl, nitro, cyano, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, imidazolyl, tetrazolyl or purinyl,

R25 is hydrogen, hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, nitro or halogen,

R26 is hydrogen, halogen, hydroxyl, nitro, 1-4C-alkyl, 1-4C-alkoxy, carboxy-1-4C-alkyl, carboxyl or 1-4C-alkoxycarbonyl,

R3 and R4 are both hydrogen or together form an additional bond,

R5 is R6 or $-C_pH_{2p}-Ar$, in which

R6 is hydrogen, 1-8C-alkyl, 3-10C-cycloalkyl, 3-7C-cycloalkylmethyl, 7-10C-polycycloalkyl, pyridyl, or an unsubstituted or by R61 and/or R62 substituted phenyl radical, in which

R61 is 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, nitro or halogen, and

R62 is 1-4C-alkyl, nitro or halogen,

Ar is an unsubstituted phenyl, naphthyl or pyridyl radical, or a phenyl radical substituted by R7 and/or R8, in which

R7 is hydroxyl, halogen, nitro, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl, and

R8 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

p is an integer from 1 to 4,

r is an integer from 1 to 8,

and the salts of these compounds.

3. Compounds of the formula I according to claim 1, in which

R1 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is hydroxyl or stands for $-O-C_rH_{2r}$-R21, wherein

R21 is chlorine, bromine, hydroxyl, carboxyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, pyrrolyl, imidazolyl, pyrazolyl, benzimidazolyl, indolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, halogen, carboxyl, carboxy-1-4C-alkyl or 1-4C-alkoxycarbonyl,

R24 is hydrogen, nitro, cyano, halogen, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, tetrazolyl, imidazolyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R26 is hydrogen, hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, carboxyl or carboxy-1-2C-alkyl,

R3 and R4 are both hydrogen or together form an additional bond,

R5 is R6 or $-C_pH_{2p}$-Ar, in which

R6 is hydrogen, 1-8C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl, bornyl, norbornyl, adamantyl, pyridyl, or an unsubstituted or by R61 substituted phenyl radical, in which

R61 is 1-2C-alkyl, 1-2C-alkoxy, carboxyl, 1-2C-alkoxycarbonyl or halogen,

Ar is an unsubstituted or by R7 substituted phenyl radical, in which

R7 is hydroxyl, halogen, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, carboxy-1-4C-alkyl, 1-4C-alkylcarbonyloxy or 1-4C-alkoxycarbonyl and

p is an integer from 1 to 2,

r is an integer from 1 to 8,

and the salts of these compounds.

4. Compounds of the formula I according to claim 1, in which

R1 is methoxy, ethoxy, difluoromethoxy or trifluoromethoxy,

R2 is hydroxyl or stands for $-O-C_rH_{2r}$-R21, wherein

R21 is chlorine, bromine, hydroxyl, carboxyl, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, pyrrolyl,

imidazolyl, pyrazolyl, benzimidazolyl, indolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is hydrogen, carboxyl or carboxy-1-2C-alkyl,

R24 is hydrogen, cyano, carboxyl, carboxy-1-2C-alkyl, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, tetrazolyl, imidazolyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R26 is hydrogen, 1-2C-alkyl or carboxy-1-2C-alkyl,

R3 and R4 form together an additional bond,

R5 is R6 or $-C_pH_{2p}$-Ar, in which

R6 is 3-7C-cycloalkyl or an unsubstituted or by R61 substituted phenyl radical, in which

R61 is carboxyl or 1-2C-alkoxycarbonyl,

Ar is an unsubstituted or by R7 substituted phenyl radical, in which

R7 is carboxyl, carboxy-1-2C-alkyl or 1-2C-alkoxycarbonyl,

p is 1,

r is an integer from 1 to 6,

and the salts of these compounds.

5. Compounds of the formula I according to claim 1, in which

R1 is methoxy,

R2 is hydroxyl or stands for $-O-C_rH_{2r}$-R21, wherein

R21 is bromine, hydroxyl, carboxyl, dimethylamino, imidazolyl, benzimidazolyl, purinyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is carboxymethyl,

R24 is hydrogen, carboxyl, carboxymethyl, aminocarbonyl, cyano, tetrazolyl, imidazolyl or 4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl,

R26 is hydrogen, methyl or carboxymethyl,

R3 and R4 form together an additional bond

R5 is 5-7C-cycloalkyl or phenyl,

r is an integer from 1 to 6,

and the salts of these compounds.

6. Compounds of the formula I according to claim 1, in which

R1 is methoxy,

R2 stands for $-O-C_rH_{2r}$-R21, wherein

R21 is hydroxyl, imidazolyl, a phenyl radical substituted by R22, a phenoxy radical substituted by R24, or a coumarinyloxy radical substituted by R26, in which

R22 is carboxymethyl,

R24 is hydrogen, carboxyl, carboxymethyl, aminocarbonyl, cyano or imidazolyl,
R26 is hydrogen, methyl or carboxymethyl,
R3 and R4 form together an additional bond,
R5 is cyclopentyl, cycloheptyl or phenyl,
r is an integer from 1 to 6,
and the salts of these compounds.

7. Compounds according to one of the preceding claims, wherein in the group $-O-C_rH_{2r}-R21$ $-C_rH_{2r}-$ is a straight chain group and r is an integer from 2 to 6.

8. Medicaments containing one or more compounds according to claim 1 together with the usual pharmaceutical auxiliaries and/or carrier materials.

9. Compounds according to claim 1 for use in the treatment of illnesses.

10. Use of compounds according to claim 1 for the production of medicaments for the treatment of airways disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/08015

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D237/32 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 634 404 A (RHONE POULENC) 18 January 1995 see page 18 ---	1
A	WO 94 12461 A (PFIZER) 9 June 1994 cited in the application see page 77; example 108 -----	1,6-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 1999	19/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/EP 98/08015

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 634404 A	18-01-1995	AU 6735194 A	27-01-1995
		BG 98899 A	31-05-1995
		BR 9402264 A	14-03-1995
		CA 2127933 A	14-01-1995
		CN 1103866 A	21-06-1995
		CZ 9401679 A	15-02-1995
		FI 943317 A	14-01-1995
		HU 67328 A	28-03-1995
		JP 7165730 A	27-06-1995
		PL 304272 A	23-01-1995
		SK 82894 A	08-02-1995
		ZA 9405095 A	22-02-1995
WO 9412461 A	09-06-1994	AU 673569 B	14-11-1996
		AU 5539694 A	22-06-1994
		CA 2150812 A	09-06-1994
		CN 1094028 A	26-10-1994
		CZ 9501417 A	15-11-1995
		EP 0672031 A	20-09-1995
		FI 935379 A	03-06-1994
		HU 65928 A	28-07-1994
		IL 107758 A	20-11-1997
		JP 8501318 T	13-02-1996
		NO 952178 A	01-08-1995
		NZ 257955 A	28-05-1996
		PL 309257 A	02-10-1995
		US 5814651 A	29-09-1998
		ZA 9308978 A	01-06-1995